PATENT SPECIFICATION (11) 1 412 017

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(21) Application No. 55587/72 (22) Filed 1 Dec. 1972

(31) Convention Application No. 206 538 (32) Filed 9 Dec. 1971

(31) Convention Application No. 245 870 (32) Filed 20 April 1972

(31) Convention Application No. 273 465 (32) Filed 20 July 1972

(31) Convention Application No. 299 840 (32) Filed 24 Oct. 1972 in

(33) United States of America (US)

(44) Complete Specification published 29 Oct. 1975

(51) INT CL² C07D 487/02 // A61K 31/505 (C07D 487/02, 231/38, 239/42, 295/00)

(52) Index at acceptance

C2C 1400 1407 1532 20Y 214 215 220 226 22Y 246 247 250 251 252 25Y 271 280 281 28X 29X 29Y 305 30Y 311 313 314 315 31Y 321 322 323 326 327 32Y 332 337 342 34Y 350 351 352 355 35Y 360 361 364 366 367 368 36Y 373 376 37X 37Y 386 43X 440 443 449 451 453 456 45X 45Y 464 470 471 500 50Y 551 574 579 601 614 620 621 623 624 625 628 62X 62Y 634 650 652 658 65X 670 671 672 675 676 677 678 679 680 681 68Y 698 708 73Y 744 761 765 776 777 77Y 790 79Y BC KF LE LT MD ML NF NG NL NR NT QL TN UK WC ZB ZF

(54) PYRAZOLO[1,5a]PYRIMIDINES

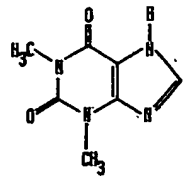
(71) We, ICN PHARMACEUTICALS INC. (previously known as International Chemical & Nuclear Corporation), a Corporation organised and existing under the Laws of the State of California, United States of America, of 171 South Lake Avenue, Pasadena, State of California, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to certain pyrazolo (1,5α) pyrimidines and to a process for the production thereof.

As reported by Sutherland et al in "Cyclic AMP", *Am. Rev. Biochem.* 37, 149 (1968), cyclic adenosine monophosphate (C—AMP) has been established as an intracellular "second messenger", mediating many of the actions of a variety of different hormones. According to this theory, first messenger hormones, epinephrine and norepinephrine, influence adenyl cyclase contained at or within cell walls to form intracellular cyclic AMP from adenosine triphosphate upon receipt of the extracellular hormone signal. The formed cyclic AMP in turn functions as a second messenger and stimulates the intracellular functions perculiar to the target cells of the hormone. Cyclic AMP has thus been shown to "activate" protein kinases, which in turn produce physiological effects such as muscle contraction, glycogenolysis, steriodogenesis and dipolysis.

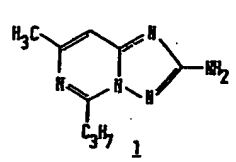
Cyclic AMP is degraded, however *in vivo* by phosphodiesterase enzymes, which catalyze hydrolysis of the cyclic purine nucleotide to 5'-adenosine monophosphate with a consequent loss of function. It has accordingly been suggested that substituted cyclic AMP analogs which are more resistant to phosphodiesterase degradation than the naturally occurring cyclic nucleotide might be administered to aid lagging cellular processes. Synthetic production of such compounds, however, is quite costly. It would be advantageous, therefore, to enhance the beneficial effects of naturally produced cyclic AMP by administering compounds which are capable of inhibiting the undesirable effects of phosphodiesterase enzymes.

Sutherland, et al, in *Circulation 37*, 279 (1968), suggests that the pharmacological effects of theophylline, which has the structure



are the result of its ability to inhibit the action of phosphodiesterase enzymes. Theophylline has thus been employed in lieu of the adenyl cyclase-stimulating hormones, epinephrine and norepinephrine, as a heart stimulant following cardiac arrest and in refractory asthma cases as a bronchial dilator. Theophylline, however, does not selectively inhibit phosphodiesterase, but rather gives general stimulation to the central nervous system. Accordingly, the use of theophylline can make the recipient nervous and irritable and can also create cardiovascular effects, i.e., rapid beating of the heart. By the same token, theophylline is not as potent as phosphodiesterase inhibitor as is desired and consequently has to be used in larger quantities, which, of course, can further the undesirable effects enumerated above.

F. L. Rose et al, in articles appearing in *J. Chem. Soc.* 5642 (1963), 3357 (1965) and 1593 (1969), reported a number of triazolo[2,3c]pyrimidines and triazolo-[4,3c]pyrazines (for example, compounds 1 and 2 shown below) which are structurally releated to theophylline and capable of protecting animals from histamine-induced bronchospasm.



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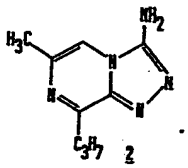

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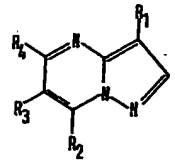
Pursuing an idea that the pharmacological effects of compounds 1 and 2 might be the result of the same biochemical mechanism as proposed for theophylline, various substituted-pyrazolo[1,5a]pyrimidines were prepared and found to possess the ability to inhibit the enzyme 3',5'-cyclic AMP phosphodiesterase. Further evaluation of these compounds has also revealed that many of these phosphodiesterase inhibitors possess significant pharmacological properties, particularly in the cardiovascular area. For example, 3-bromo-5,7-dimethylpyrazolo[1,5a]pyrimidine and 3-bromo-5-methyl-7-*n*-propylpyrazolo[1,5a]pyrimidine not only are significantly more active than theophylline against various phosphodiesterase enzymes, but also have the ability to produce a positive inotropic effect in an anesthesized dog without significantly altering heart rate or blood pressure.

According to the present invention there is provided a compound of the structure



wherein R_1 is H, alkoxycarbonyl, alkyl, carbonitrile, halogen, carbamoyl, acyl, aminomethyl, dialkylaminomethyl, nitro, amino, or acetamido; R_2 is alkyl, C_1 to C_8 linear or branched chain alkoxy, C_1 to C_8 alkylthio, SH, or alkyl or dialkylamino, cyclic amino or substituted amino; R_3 is H; and R_4 is H, alkyl, or phenyl; provided that when R_2 and R_4 are methyl, R_1 is not H or carbethoxy; when R_4 is CH_3 and R_2 is methoxy or ethoxy, R_1 is not H; and when R_2 is CH_3, R_4 and R_1 are not both H; and when R_2 is hydrazino and R_4 is phenyl, R_1 is not H.

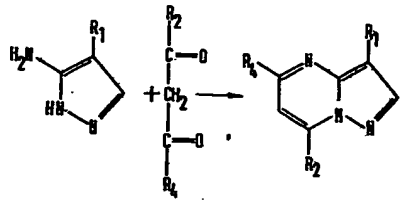
Unless otherwise indicated the alkyl substituents preferably contain from 1 to 8 carbon atoms, more preferably from 1 to 6 carbon atoms, and may be branched or linear groups. The alkoxy substituents are C_1 to C_8, but preferably C_1 to C_4, linear or branched alkoxy groups. Where R_2 in an alkylthio group, groups having from 1 to 3

carbon atoms are especially preferred. Suitable substituted amino groups are dialkoxyalkylamino, carboxyalkylamino, hydroxyalkylamino, hydrazyl or alkylidenohydrazyl groups, while suitable cyclic amino groups include the morpholino group and the piperidino group.

The compounds of this invention and the general procedure utilized in preparing the same are illustrated and will be described in conjunction with the schematic drawings which follow. The starting materials utilized in this invention are 3-aminopyrazole (1), 3-amino-4-carbethoxypyrazole (2), 3-amino-4-cyanopyrazole (3), 3-amino-4-pyrazolecarboxamide (4), 3-amino-4-ethylpyrazole (5), 3-amino-4-bromopyrazole (6), and 3-amino-4-nitropyrazole (7). All of these starting materials have been previously reported in the literature with the exception of 3-amino-4-ethylpyrazole (5), which is prepared in the following manner. The base catalyzed condensation of *n*-butyronitrile with ethyl formate affords *α*-formyl-*n*-butyronitrile, which when treated *in situ* with hydrazine hydrate, affords 3-amino-4-ethylpyrazole (5) as a colorless oil.

For convenience, only certain compounds related to those of the invention have been included in the description which follows.

REACTION SCHEME I



(1) $R_1 = H$

(2) $R_1 = COOC_2H_5$

(3) $R_1 = C \equiv N$

(4) $R_1 = CONH_2$

(5) $R_1 = C_2H_5$

(8) $R_2 = R_4 = CH_3$; $R_1 = H$

(9) $R_2 = R_4 = CH_3$; $R_1 = COOC_2H_5$

(10) $R_2 = R_4 = CH_3$; $R_1 = C \equiv N$

(11) $R_2 = R_4 = CH_3$; $R_1 = CH_2-NH_2$

(12) $R_2 = R_4 = CH_3$; $R_1 = CONH_2$

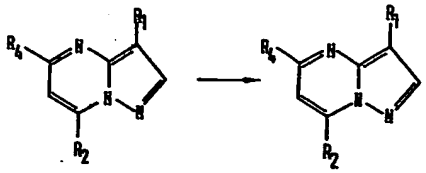
(13) $R_2 = R_4 = CH_3$; $R_1 = C_2H_5$

(14) $R_2 = R_4 = C_2H_5$; $R_1 = H$

(15) $R_2 = R_4 = C_3H_7$; $R_1 = H$

The general procedure for preparation of the 5,7-dialkylpyrazolo[1,5a]pyrimidines follows the work of Y. Makisumi, *Chem. Pharm. Bull* (Tokyo), *10*, 612 (1962), and is depicted in Reaction Scheme I. 3-Aminopyrazole (1) and 3-amino-4-carbethoxypyrazole (2) are condensed with pentane-2,4-dione to provide 5,7-dimethylpyrazolo-[1,5a]pyramidine (8) and the corresponding 3-carbethoxy derivative (9). This reaction has been extended to include the additional 3-amino-4-substituted pyrazoles (3, 4, and 5) to provide the 3-cyano (10), 3-carboxamido (12), and 3-ethyl (13) derivatives of 5,7-dimethylpyrazolo[1,5a]pyrimidine. The catalytic reduction of 3-cyano-5,7-dimethylpyrazolo[1,5a]pyrimidine (10) affords the corresponding 3-aminoethyl-5,7-dimethylpyrazolo[1,5a]pyrimidine (11). Additionally, it has been found that the condensation of 3-aminopyrazole (1) with heptane-3,5-dione and nonane-4,6-dione affords excellent yields of 5,7-diethylpyrazolo[1,5a]pyrimidine (14) and 5,7-di-*n*-propylpyrazolo[1,5a]pyrimidine (15), respectively.

REACTION SCHEME II



(8) $R_2 = R_4 = CH_3$; $R_1 = H$

(14) $R_2 = R_4 = C_2H_5$; $R_1 = H$

(15) $R_2 = R_4 = n\text{-}C_3H_7$; $R_1 = H$

(16) $R_2 = R_4 = CH_3$; $R_1 = Br$

(17) $R_2 = R_4 = CH_3$; $R_1 = Cl$

(18) $R_2 = R_4 = CH_3$; $R_1 = I$

(19) $R_2 = R_4 = CH_3$; $R_1 = F$

(20) $R_2 = R_4 = CH_3$; $R_1 = COCH_3$

(21) $R_2 = R_4 = CH_3$; $R_1 = CH_2\text{–}N(CH_3)_2$

(22) $R_2 = R_4 = CH_3$; $R_1 = NO_2$

(23) $R_2 = R_4 = CH_3$; $R_1 = NH_2$

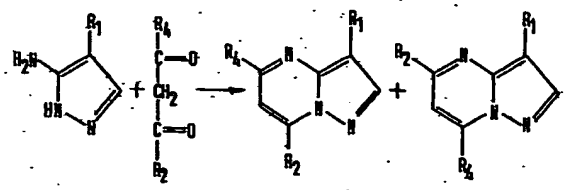
(24) $R_2 = R_4 = CH_3$; $R_1 = NHCOCH_3$

(25) $R_2 = R_4 = C_2H_5$; $R_1 = Br$

(26) $R_2 = R_4 = n\text{-}C_3H_7$; $R_1 = Br$

The 3-unsubstituted-5,7-dialkylpyrazolo[1,5a]pyrimidines (8, 14, and 15) readily undergo electrophilic attack at the 3-position as shown in Reaction Scheme II. The treatment of the 5,7-dialkylpyrazolo[1,5a]pyrimidines (8, 14, or 15) with N-bromosuccinimide results in the formation of 3-bromo-5,7-dialkylpyrazolo[1,5a]pyrimidines (16, 25, 26). Additionally, it has been found that the treatment of (8) with N-chlorosuccinimide or with iodine monochloride results in the formation of the 3-chloro (17) and the 3-iodo (18) derivatives of 5,7-dimethylpyrazolo[1,5a]pyrimidine. The reaction of 5,7-dimethylpyrazolo[1,5a]pyrimidine (8) with trifluoroacetic acid and boron trifluoride etherate has been found to afford 5,7-dimethyl-3-fluoro-pyrazolo[1,5a]pyrimidine (19). Friedel-Crafts acylation of 5,7-dimethylpyrazolo[1,5a]pyrimidine (8) affords 3-acetyl-5,7-dimethylpyrazolo[1,5a]pyrimidine (20) in 61% yields. When compound 8 is treated with an aqueous solution of dimethylamine and formalin solution, 5,7-dimethyl-3-dimethylaminomethylpyrazolo[1,5a]pyrimidine (21) is obtained. Finally, nitration of compound 8 affords the expected 5,7-dimethyl-3-nitropyrazolo[1,5a]pyrimidine (22). Reduction of compound 22 with palladium or charcoal catalyst affords the corresponding 3-amino-5,7-dimethylpyrazolo[1,5a]pyrimidine (23), which when treated with acetic anhydride results in the formation of the 3-acetamido derivative (24). The site of electrophilic attack at position 3 in these 5,7-dialkylpyrazolo[1,5a]pyrimidines has been proven by the proton magnetic resonance spectra, since the up-field proton at 6.60% (which is coupled to the proton at 8.11%; J=0.0066%) found in 5,7dimethylpyrazolo[1,5a]pyrimidine (8) is absent in these 3-substituted derivatives.

REACTION SCHEME III



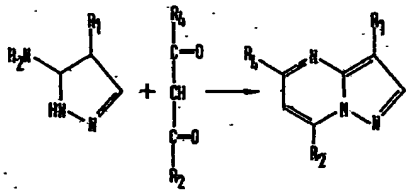
(27) (28)

(1) $R_1 = H$ (27a) $R_2 = CH_3$; $R_4 = C_2H_5$; $R_1 = H$

(27b) $R_2 = CH_3$; $R_4 = C_3H_7$; $R_1 = H$

(28a) $R_2 = C_2H_5$; $R_4 = CH_3$; $R_1 = H$

(28b) $R_2 = n\text{-}C_3H_7$; $R_4 = CH_3$; $R_1 = H$



(2) $R_1 = COOC_2H_5$ (29) $R_2 = C_2H_5$; $R_4 = CH_3$; $R_1 = Br$

(30) $R_2 = n\text{-}C_3H_7$; $R_4 = CH_3$; $R_1 = Br$

(31) $R_2 = C_2H_5$; $R_4 = CH_3$; $R_1 = NO_2$

(32) $R_2 = C_2H_5$; $R_4 = CH_3$; $R_1 = COOC_2H_5$

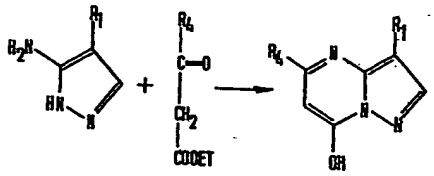
(33) $R_2 = CH_3$; $R_4 = C_6H_5$; $R_1 = H$

The condensation of 3-aminopyrazole (1) with unsymmetrical β-diketones is shown in Reaction Scheme III. The reaction of 3-aminopyrazole (1) with hexane-2,4-dione affords a mixture of the isomers 27a and 28a. Because of similarity of the physical properties of these two isomers, separation is difficult and for that reason the crude isomeric mixture of 27a and 28a was converted into higher melting derivatives (29) and (31), which may be isolated by column chromatography and fractional recrystallization techniques. Similarly, condensation of 3-aminopyrazole (1) with heptane-2,4-dione affords a mixture of the isomers 27b and 28b, which, when treated with N-bromosuccinimide, affords 3 - bromo - 5 - methyl - 7 - *n* - propylpyrazolo[1,5a]-pyrimidine (30) which is purified by chromatography. The condensation of 3-amino-4-carbethoxypyrazole (2) with hexane-2,4-dione results in a mixture of isomeric products; however, 3 - carbethoxy - 7 - ethyl - 5 - methylpyrazolo[1,5a]pyrimidine (32) has been found to be the predominate isomer. By the same token, condensation of 1-phenyl-1,3-butane-dione with 3-aminopyrazole (1) yields an isomeric product which may be recrystallized without chromatography to yield 7-methyl-5-phenyl-pyrazolo[1,5a]pyrimidine (33). That this isomer was obtained rather than 5-methyl-7-phenylpyrazolo[1,5a]pyrimidine was demonstrated by comparison of physical data (proton magnetic resonance spectra, ultra-violet spectra, and melting point) with the 5-methyl isomer that was previously reported by H. Dorn et al, *J. Prak, Chem.*, 313, 969 (1971).

The structural assignment of compounds 29—32 is based on the proton magnetic resonance spectra of the well separated C_5 and C_7 methyl signals. It has been demonstrated [H. Reimlinger, *Chem. Ber.*, *103*, 1900 and 3252 (1970), *104*, 2232 and 2237 (1971)] that in 5,7-dimethylpyrazolo[1,5a]pyrimidine (8) the C_7 methyl signal, being adjacent to the bridgehead nitrogen, is deshielded to a greater extent than the C_5 methyl signal (adjacent the N_4 nitrogen) and thus occurs at a lower field. The assignments are 2.56δ for C_5-methyl and 2.73δ for the C_7-methyl in deuterochloroform. Since the replacement of a longer alkyl chain (e.g. ethyl or propyl) for one methyl group at either C_5 or C_7 would not be expected to change the chemical shift of the remaining methyl group, the 5,methyl-7-alkyl isomer can be distinguished from the 7-methyl-5-alkyl isomer via pmr (in deuterochloroform) and the percentage of each isomer in the isomeric mixture can be estimated from the integration of the signals. Similarly, the C_5-methyl signal occurs at 2.60δ and the C_7-methyl signal at 2.72δ (in deuterochloroform) for the pmr of 3-bromo-5,7-dimethylpyrazolo[1,5a]pyrimidine (16), thus permitting identification of the separated products 29 and 30 from the bromination (and subsequent chromatography) of the isomeric mixtures 27a and 28b or 27b and 28b.

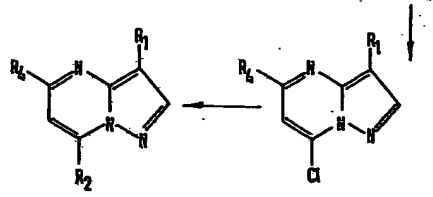
The condensation of 3-amino-4-substitutedpyrazoles with β-ketoesters is shown in Reaction Scheme IV. Following the procedure described by Y. Makisumi, *Chem. Pharm. Bull.* (Tokyo), *10*, 612 and 620 (1962), 3-aminopyrazole (1) was condensed with acetoacetic ester to obtain 5-methyl-7-hydroxypyrazolo[1,5a]pyrimidine (34) which, when treated with phosphorus oxychloride, results in the formation of 7-chloro-5-methylpyrazolo[1,5a]pyrimidine (36). These reactions have been extended to 3-amino-4-ethylpyrazole (5) to afford 3-ethyl-7-hydroxy-5-methylpyrazolo[1,5a]pyrimidine (35) and the corresponding 7-chloro-3-ethyl-5-methylpyrazolo[1,5a]-pyrimidine 36a. The chloro moieties of compounds 36 and 36a are quite susceptible to nucleophilic displacement when treated with various nucleophilic reagents.

REACTION SCHEME IV

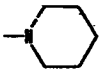


(1) R_1 = H (34) R_4 = CH_3; R_1 = H

(5) R_1 = C_2H_5 (35) R_4 = CH_3; R_1 = C_2H_5



(37) R_1 = H; R_4 = CH_3; R_2 = $N(C_2H_5)_2$ (36) R_4 = CH_3; R_1 = H

(38) R_1 = H; R_4 = CH_3; R_2 =  (36a) R_4 = CH_3; R_1 = C_2H_5

(39) R_1 = H; R_4 = CH_3; R_2 = $NH(CH_2)_7CH_3$

(40) R_1 = H; R_4 = CH_3; R_2 = $NH-NH_2$

(41) R_1 = H; R_4 = CH_3; R_2 = $NH-N=C(CH_3)_2$

(42) R_1 = H; R_4 = CH_3; R_2 = $NH-CH_2-CH_2OH$

(43) R_1 = H; R_4 = CH_3; R_2 = $NH-CH_2-COOH$

(44) R_1 = H; R_4 = CH_3; R_2 = OCH_2-CH_3

(45) R_1 = C_2H_5; R_4 = CH_3; R_2 = $NH-CH_2-CH_2-CH_3$

(46) R_1 = C_2H_5; R_4 = CH_3; R_2 = $OCH_2-CH_2-CH_3$

(47) R_1 = C_2H_5; R_4 = CH_3; R_2 = SCH_2-CH_3

(48) R_1 = Br; R_4 = CH_3; R_2 = $NH-CH_2-CH_2-CH_2-CH_3$

(49) R_1 = Br; R_4 = CH_3; R_2 = $NH-CH_2-CH_2(OCH_3)_2$

Thus, the treatment of compounds 36 or 37 with various amines, sodium alkoxides, and sodium alkylmercaptides results in the formation of the 7-substituted derivatives 37 to 40 and 42 to 47. The reaction of 7-hydrazino-5-methylpyrazolo[1,5a]pyrimidine (40) with acetone in ethanolic hydrogen chloride results in the formation of the isopropylidene derivative (41). These 5-methyl-7-substitutedpyrazolo[1,5a]pyrimidines readily undergo electrophilic attack at the 3 position. Thus, in this manner, the 3-bromo-5-methyl-7-substitutedaminopyrazolo[1,5a]pyramidines (48) and (49) have been prepared.

The invention will now be further described and illustrated in the following Examples (aside from Example I which merely serves to illustrate the preparation of one starting material, 3-amino-4-ethylpyrazole) in which all parts and percentages are by weight and all temperatures in degrees Centigrade unless otherwise indicated. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infra-red and nuclear magnetic resonance spectra were determined on a Perkin-Elmer 257 grating infra-red spectrophotometer and on a Hitachi Perkin-Elmer R—20A high resolution nuclear magnetic resonance spectrophotometer, respectively. (Hitachi is a Registered Trade Mark). Hydrogenations were carried out on a Parr hydrogenator at room temperature and at a starting pressure of 42 lbs/in² of hydrogen. All samples displayed a single spot on thin layer chromatography and were analyzed by the Heterocyclic Chemical Corporation of Harrisonville, Missouri. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

Examples XXV to XXIX relate to the preparation of intermediate derivatives.

EXAMPLE I.

Preparation of 3-Amino-4-ethylpyrazole (5)

A suspension of sodium metal [53.0g; 2.31 formula weights] in 1500 ml of anhydrous ether was stirred at 20° while a mixture of ethyl formate [180.0g; 2.43 moles] and *n*-butyronitrile [158.0g; 2.31 moles] was added dropwise over a period of two hours. After the addition was complete, the mixture was stirred at 20—25° for two days at which time the sodium metal was completely reacted. The reaction mixture was cooled to 10° and neutralized by the dropwise addition of glacial acetic acid [138.0g; 2.31 moles]. The temperature of the mixture during neutralization was maintained at 10—15°. The solids were separated by filtration and the filtrate evaporated to dryness at reduced keeping the temperature below 20°. The resulting crude α-formyl n-butyronitrile was utilized directly for the formation of 3-amino-4-ethylpyrazole (7) without further purification.

The crude α-formyl n-butyronitrile was dissolved in 200 ml of ethanol and treated with 85% hydrazine hydrate [118g; 2.0 formula weights] and 36 ml of glacial acetic acid. The resulting solution was heated at reflux for two hours and then evaporated to dryness. The residual oil was purified by distillation at 0.2mm (Hg.). The fraction that had a boiling point of 120—4° was collected. This fraction weighed 55.2g (21%) and was found to be analytically pure 3-amino-4-ethylpyrazole (7). Analysis corresponds to that calculated for $C_5H_9N_3$:(C,H).

EXAMPLE II.

5-7-Dimethyl pyrazolo[1,5a]pyrimidine-3-carbonitrile (10)

A solution of 7.25g (0.067 moles) 3-amino-4-cyanopyrazole [R.K. Robins, J.A.C.S. *78*, 788 (1956)], acetylacetone [7.00 g (0.07 moles)], piperidine (10 drops) in 100 ml of EtOH was heated at reflux. After refluxing 6 hrs. the solution was allowed to cool slowly, whereupon crystallization occurred. The product was separated by filtration and recrystallized from EtOH to afford 6.00 g. (52%) of analytically pure product; mp 165—7°.

Anal. corresponds to that calculated for ($C_9H_8N_4$) C, H, N.

IR. (KBr) 2250 cm^{-1} (CN)

EXAMPLE III.

3-Aminomethyl-5,7-dimethyl pyrazolo[1,5a]pyrimidine hydrochloride (II)

To a solution of the carbonitrile product of Example II (1.00 g) in 150 ml of EtOH was added 5 ml of HCl (12*N*) and 0.25g of 10% Pd/C catalyst. The resulting mixture was hydrogenated at room temperature for 16 hrs. The mixture was filtered through Celite and evaporated to dryness at reduced pressure. (Celite is a Registered Trade Mark). The gummy semi-solid was dissolved in water (25 ml), made basic by the addition of NaOH solution (1*N*), and extracted into $CHCl_3$ solution, and after drying, was chromatographed on basic alumina. Evaporation of the $CHCl_3$ eluant afforded a colorless solid (mp 119—20°) that rapidly became colored. The hydrochloride of the solid was prepared by dissolving the same in Et_2O and adding HCl gas; mp 265—7° (dec).

Anal. Corresponds to that calculated for ($C_9H_{12}N_4$. HCl) C, H, N.

EXAMPLE IV.

5,7-Dimethyl pyrazolo[1,5a]pyrimidine-3-carboxamide (12)

A mixture of 1.00g (5.7 mmoles) 3-amino-4-carbamoylpyrazole, hemisulfate [R.K. Robins, J.A.C.S. *78*, 788 (1956)], acetylacetone [0.60g (6.0 mmoles)], piperidine (1.5g) in 40 ml of EtOH was heated at reflux. After refluxing 16 hrs. the solution was allowed to cool. The crystalline product was recrystallized from EtOH to yield 0.90g (83%) of analytically pure product; mp 247—8° (dec).

Anal. Corresponds to that calculated for ($C_9H_{10}N_4O$) C, H, N.

IR. (KBr) 1665 cm^{-1} ($CONH_2$)

NMR. (d_6-DMSO) singlets in a ratio of 3:3:1:2:1, with chemical shifts of 2.62δ (CH_3), 2.75δ (CH_3), 7.18δ and 8.52δ (ring protons), and 7.50δ (broad, NH_2 of amide).

EXAMPLE V.

Preparation of 5,7-Dimethyl-3-Ethylpyrazolo[1,5a]Pyrimidine (13)

A solution of 3-amino-4-ethylpyrazole (1) [1.0g; 10 mmoles], 2,4-pentanedione [1.0g; 9 mmoles], and 3 drops of piperidine in 5 ml of absolute ethanol was heated at reflux for 12 hours. The resulting solution was evaporated to dryness, and the residual oil was purified by column chromatography on silica gel (50g) utilizing a mixture of 30—60° petroleum ether: chloroform (7:3) as the solvent. Evaporation of the solvent afforded 1.3g (82%) of analytically pure 5,7-dimethyl-3-ethylpyrazolo-[1,5a]pyrimidine (5) as a colorless oil.

Anal. Corresponds to that calculated for ($C_{10}H_{13}N_3$) C, H, N

EXAMPLE VI.

5,7-Diethylpyrazolo[1,5a]pyrimidine (14)

This compound was prepared from 6.5 g (0.05 mol) of heptane-3,5-dione and the yield of chromatographed material (white needles, m.p. 43—44°C from petroleum ether was 6.3 g (72%).

Anal. calcd for $C_{10}H_{13}N_3$(MW 175): C, 68.54; H, 7.48; N, 23.98;
Found: C, 68.52; H, 7.58; N, 24.25

NMR($CDCl_3$) m, 1.48 (both C_5-ethyl and C_7-ethyl triplets); m, 3.18 (both C_6-ethyl and C_7-ethyl quartets); s, 6.58δ (C_6—H); s, 6.68 (C_3—H) and s, 8.18 (C_2—H), the latter two protons being coupled with $J_{2,3}$=1.9 cps.

EXAMPLE VII.

5,7-Di-n-propylpyrazolo[1,5a]pyrimidine (15)

This compound was synthesized from nonane-4,6-dione (15.6 g, 0.10 mole) to give 17.0 g (84%) of a pale yellow oil, after chromatography.

Anal. calcd for $C_{12}H_{17}N_3$(MW 203): C, 70.93; H, N, 20.69. Found: C. 71.16; H, 8.25; N, 20.85. b.p. 155—158°/0.^{1mm}

EXAMPLE VIII.

3-Bromo 5,7-dimethyl pyrazolo[1,5a]pyrimidine (16)

To a solution of 2.0g (13.6 mmoles) 5,7-dimethyl pyrazolo[1,5a]pyribidine [Y. Makisumi, Chem. Pharm. Bull. (Tokyo) *10*, 612 (1962)] in $CHCl_3$ (25 ml) was added N-bromosuccinimide (NBS) [2.42g (13.6 mmoles)]. This mixture was heated on the steam bath for 10 minutes, and then allowed to cool to room temperature. The clear yellow solution was then added to an ice cold solution of potassium hydroxide (50 ml, 2*N*) with vigorous stirring. The $CHCl_3$ layer was dried over Na_2SO_4, then chromatographed on basic alumina. Evaporation on the $CHCl_3$ eluant afforded a white solid which was further purified by recrystallization from petroleum ether (30—60°) to give 1.7g (56%) of analytically pure product; mp 115—6°.

Anal. Corresponds to that calculated for ($C_9H_8N_3Br$) C, H, N.

NMR ($CDCl_3$) four singlets in a ration of 3:3:1:1 at 2.60δ (CH_3), 2.72δ (CH_3), 6.62δ (H at 6 position), and 8.10δ (H at 2 position). The spectrum of the starting material exhibited peaks at 2.56δ (CH_3 at C_7), 2.73δ (CH_3 at C_5), 6.58δ (C_6—H), 6.60δ (C_3—H), and 8.11δ (C_2—H) (protons at C_2 and C_3 were coupled, J=2.1cps).

EXAMPLE IX.

3-chloro-5,7-dimethyl pyrazolo[1,5a]pyrimidine (17)

In a manner similar to the preparation of Example VIII the treatment of 5,7-dimethyl pyrazolo[1,5a]pyrimidine [1.20g (8.15 mmoles)] with N-chlorosuccinimide (NCS) [1.33g (10.0 mmoles)] afforded 963 mg (65%) of analytically pure product; mp 89—90°.

Anal. Corresponds to that calculated for ($C_9H_8N_3Cl$) C, H. N.

EXAMPLE X.

5,7-dimethyl 3-iodo pyrazolo[1,5a]pyrimidine (18)

A solution of ICl [5.0g (27 mmoles)] in $CHCl_3$ (50 ml) was added to a stirred solution of 5,7-dimethyl pyrazolo[1,5a]pyrimidine [2.96g (20 mmoles)] in $CHCl_3$ (50 ml). Within a few minutes, the mixture became warm and crystals of the hydrochloride salt of the subject compound began to separate. The mixture was warmed on the steam bath for 2—3 min to complete the reaction, and then refrigerated overnight. The yellow hydrochloride salt was separated by filtration, washed with Et_2O, and the air dried. The yellow solid, which weighed 4.4g, was dissolved in water (100 ml) and this solution was made alkaline by the addition of NaOH solution (2.5*N*). The alkaline solution was extracted with $CHCl_3$ 3(25 ml), and the $CHCl_3$ extracts were dried over Na_2SO_4. The $CHCl_3$ extract was chromatographed on basic alumina, and the $CHCl_3$ eluant evaporated to dryness. The residue was recrystallized from petroleum ether (30—60°) to afford 2.02g (37%) of analytically pure product; mp 120—2°.

Anal. Corresponds to that calculated for ($C_8H_8N_3I$) C, H, N.

EXAMPLE XI.

5,7-Dimethyl 3-Fluoro pyrazolo[1,5a]pyrimidine (19)

A mixture of 5,7-dimethyl pyrazolo[1,5a]pyrimidine [1.47g (10 mmoles)], trifluoroacetic anhydride (2.0 ml), and boron trifluoride etherate (2.0 ml) in CH_2Cl_2 (30 ml) was heated at reflux for 24 hours. At the end of this time the red solution was cooled and added to an ice cold solution of NaOH (30 ml, 2*N*). The organic layer was separated and the alkaline layer extracted with CH_2Cl_2 3(20 ml). The combined CH_2Cl_2 extracts were washed with water 2(20 ml) and dried over Na_2SO_4. The CH_2Cl_2 extract was evaporated and the residue covered with n-pentane and chilled. The yellow white crystalline plates were spearated by filtration, and recrystallized from n-heptane to yield and analytically pure product; mp 129—30°.

Anal. Corresponds to that calculated for ($C_8H_8N_2F$) C, H, N, F.

NMR ($CDCl_3$) four singlets in a ratio of 3:3:1:1 at 2.55δ (CH_3), 2.60δ (CH_3), 6.60δ (H at 6 position) and 8.60δ (H at 2 position).

EXAMPLE XII.

3-Acetyl-5,7-dimethyl pyrazolo[1,5a]pyrimidine (20)

With good stirring, a solution of $SnCl_4$ [5.21 g (20 mmoles)] in CH_2Cl_2 (10 ml) was added dropwise to a solution of 5,7-dimethyl pyrazolo [1,5a]pyrimidine [2.94 g (20 mmoles)] and acetyl chloride [1.56 g (20 mmoles)] in CH_2Cl_2 (10 ml). After the addition was complete, the mixture was heated at reflux for 12 hrs., cooled, and then added to dilute HCl (100 ml, 3*N*). The organic layer was separated and the acidic solution extracted with CH_2Cl_2 2(20 ml). The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in benzene and chromatographed on basic alumina, and the benzene eluant evaporated to dryness. Recrystallization of the crystalline residue from a benzene-heptane mixture afforded 2.32 g (61%) of analytically pure product; mp 179—80°.

Anal. Corresponds to that calculated for ($C_{10}H_{11}N_3O$) C, H, N.

EXAMPLE XIII.

3-Dimethylaminomethyl-5,7-dimethyl pyrazolo[1,a]pyrimidine, dihydrochloride (21)

An aqueous solution of dimethylamine (4.0 ml, 40%) was added slowly to HOAc (4.5 ml) keeping the temperature below 10°. After the addition was complete, formalin solution (3.0 ml, 37%) was added to the solution. The resulting solution was allowed to stir for 20 min., and then 5,7-dimethyl pyrazolo[1,5a]pyrimidine [2.0 g (13.6 mmoles)] was added in small portions. The resulting mixture was then stirred at room temperature for 12 hrs. and then added to cold NaOH solution (50 ml, 2.5 *N*). This basic mixture was then extracted with $CHCl_3$ 3(50 ml), and the combined $CHCl_3$ extracts were dried over Na_2SO_4, and evaporated to dryness. The resulting oil, which did not solidify, was dissolved in Et_2O and the dihydrochloride salt of the product was precipitated by adding HCl gas. This crude product was purified by recrystallization from EtOH—EtOAc to obtain an analytically pure product; mp 194—5°.

Anal. Corresponds to that calculated for ($C_{22}H_{16}N_4 \cdot 2HCl$) C, H, N.

NMR (free amine, $CDCl_3$) seven singlets in a ratio of 3:3:3:2:1:1 at 2.21δ, 2.30δ (N—CH_3 groups), 2.59δ, 2.72δ (CH_3), 3.70δ (CH_2) 6.59 (H at 6 position), and 8.10δ (H at 2 position).

EXAMPLE XIV.

5,7-Dimethyl-3-nitro pyrazolo[1,5a]pyrimidine (22)

5,7-dimethyl pyrazolo[1,5a]pyrimidine [1.0 g (6.8 mmoles)] was dissolved in H_2SO_4 (10 ml) keeping the temperature below 5°. Fuming HNO_3 [4 ml; sp. gr. 1.5] was added dropwise to the cold H_2SO_4 solution, with good stirring. The temperature during this addition was maintained below 10°. After the addition was complete the solution was stirred at room temperature for 45min. and then added to 100 g of ice. The precipitated product was separated by filtration, washed well with H_2O, and dried. Recrystallization from CH_3OH afforded 0.75 g (57%) of analytically pure product; mp 156—7°.

Anal. Corresponds to that calculated for $C_8H_8N_4O_2$) C, H, N.

NMR ($CDCl_3$) singlets in a ratio of 3:3:1:1 at 2.80δ (CH_3), 2.85δ (CH_3), 7.04δ (H at 6 position), and 8.76δ (H at 2 position).

EXAMPLE XV.

3-Amino-5,7-dimethyl pyrazolo[1,5a]pyrimidine (23)

To a solution of the nitro derivative of Example XXII [5.0 g (26 mmoles)] in EtOH (50 ml) was added HOAc (5 ml) and 0.25 g of 10% Pd/C catalyst. The resulting mixture was hydrogenated at room temperature for 16 hours. The mixture was filtered through Celite and evaporated to dryness at reduced pressure. The oil residue was dissolved in water (100 ml), made basic with NH_4OH, and then extracted into $CHCl_3$ 3(35 ml). The combined $CHCl_3$ extracts were dried over Na_2SO_4, and chromatographed on basic alumina. Evaporation of the $CHCl_3$ eluant afforded 2.7 g (64%) of red crystalline product; mp 133—5° (dec).

Anal. Corresponds to that calculated for ($C_8H_{10}N_4$) C, H, N.

EXAMPLE XVI.

3-Acetamido-5,7-dimethyl pyrazolo[1,5a]pyrimidine (24)

A solution of the 3-amino derivative of Example XV [2.6 g (16 mmoles)] in Ac_2O (50 ml) was heated on the steam bath for ten minutes and then allowed to cool to room temperature. The crystalline product was separated by filtration, washed with H_2O and dried. Recrystallization from H_2O afforded 2.6 g (80%) of analytically pure product; mp 175—6°.

Anal. Corresponds to that calculated for ($C_{10}H_{12}N_4O$) C, H, N.

EXAMPLE XVII.

3-Bromo-5,7-diethylpyrazolo[1,5a]pyrimidine (25)

This compound was prepared by bromination of 1.75 g (0.01 mole) of the dialkyl compound. Chromatography on basic alumina with chloroform gave 2.0 g (79%) of white needles, m.p. 64—65°C.

Anal. calcd for $C_{10}H_{12}N_3Br$ (MW 254): C, 47.24; H, 4.72; N, 16.53.
Found: C, 47.10; H, 4.63; N, 16.71.

NMR ($CDCl_3$) t, 1.35δ and t, 1.43δ (from C_5- and C_7-ethyl); q, 2.98δ and q, 3.10δ from C_5- and C_7-ethyl); s, 6.63δ (C_6—H) and s, 8.08δ (C_2—H) integration 3:3:2:2:1:1. No coupling was observed for singlets at 6.63δ and 8.08δ.

EXAMPLE XVIII.

3-Bromo-5,7-di-n-propylpyrazolo[1,5a]pyrimidine (26)

This compound was prepared by brominating 4.06 g (0.02 mol) of the 5,7-di-n-propyl parent compound to yield 3.5 g (62%) of white needles, m.p. 66—67°C after chromatography on basic alumina (chloroform) and recrystallization from petroleum ether.

Anal. calcd for $C_{12}H_{18}N_3Br$ (MW 282): C, 51.06; H, 5.67; N, 14.89.
Found: C, 50.85; H, 5.92; N, 15.11.

NMR ($CDCl_3$) propyl groups appear as overlapping multiplets at 1.2δ, 1.8δ and 3.0δ; s, 6.60δ (C_6—H); s, 8.08 (C—H). Integration 6:4:4:1:1.

EXAMPLE XIX.

5-Methyl(ethyl)-7-ethyl(methyl)pyrazolo[1,5a]pyrimidine (27a & 28a)

The compound was prepared, as described above, from 3-aminopyrazole (8.3 g) and hexane-2,4-dione (11.4 g) in ethanol with a catalytic amount of piperidine. The product was isolated as a colorless oil (14.0 g, 87% yield) via chromatography on basic alumina with benzene. Oil, b.p. 173—177°/0.1mm. Mass spectrum M+=161.

Anal. Calcd. for $C_9H_{11}N_3$(MW 161): C, 67.08; H, 6.83; N, 26.08.
Found: C, 66.88; H, 6.94; N, 26.22.

NMR ($CDCl_3$) indicated two isomers, 5-ethyl-7-methyl and 5-methyl-7-ethyl, with the dominant (65.35) being the latter isomer: m, 1.4δ (two triplets from the 5-ethyl and the 7-ethyl), m, 3.1δ (two quartets from the 5-ethyl and the 7-ethyl), s, 2.56δ (C_5—CH_3) and s, 2.73δ (C_7—CH_3), s, 6.58δ (C_6—H) and coupled s, 6.60δ (C_6—H) with coupled s, 8.11δ (C_2—H) and $J_{2,3}$=1.9 cps.

EXAMPLE XX.

5-Methyl(n-propyl)-7-n-propyl(methyl)pyrazolo[1,5a]pyrimidine (27b & 28b)

This compound was prepared from heptane-2,4-dione (8.2 g, 0.064 mole) and the dominant isomer was found to be the 5-methyl-7-n-propyl. Yield: 15 g mixed isomers (86%) colorless, semisolid, mp 40—45°, b.p. 165—169°/0.1 mm. Mass spectrum M^+=175.

Anal. calcd for $C_{12}H_{17}N_3$(MW 175): C, 68.54; H, 7.48; N, 23.98.
Found: C, 68.31; H, 7.56; N, 23.79.

NMR ($CDCl_3$) m, 1.2δ ($C_{5'}$, $C_{7'}$-propyl); m, 1.8δ (C_6, $C_{7'}$-propyl); m, 3.0δ (C_5, $C_{7'}$-propyl); s, 2.58δ (C_5—CH_3) and s, 2.72δ (C_7—CH_3); s, 6.58δ (C_6—H) and coupled s, 6.63δ (C_6—H) with coupled s, 8.10δ (C_2—H) $J_{2,3}$=1.9 cps.

EXAMPLE XXI.

3-Bromo-7-ethyl-5-methylpyrazolo[1,5a]pyrimidine (29)

This compound was prepared from 2.6δ (0.063 mole) of the isomeric mixture of dialkyl compound to yield 2.5 g (64%) of the pure 7-ethyl-5-methyl isomer, m.p. 78—79°C.

Anal. Calcd for $C_9H_{10}N_3Br$ (MW 240): C, 45.00; H, 4.16; N, 17.50.
Found: C, 44.79; H, 4.38; N, 17.40.

NMR ($CDCl_3$) t, 1.43δ (ethyl); s, 2.6δ (C_5—CH_3); q, 3.10δ (ethyl); s, 6.63δ (C_6—H); s, 8.10δ (C_2—H).

The establishment of the isomer which was isolated, is based on the nmr data of 3-bromo-5,7-dimethylpyrazolo[1,5a]pyrimidine, which consist of methyl peaks at 2.60δ and at 2.72δ. The peak at 2.60δ is attributed to the C_5—CH_3, i.e., the methyl group closest to the N_4-nitrogen not involved in the bridgehead. The peak at 2.72δ is attributed to the C_7—CH_3, i.e., the methyl group closest to the bridgehead nitrogen by virtue of its greater deshielding effect, which is in accord with similar studies by other authors [Y. Makisumi, et al, *Chem. Pharm. Bull., 12,* 204 (1964)].

EXAMPLE XXII.

3-bromo-5-methyl-7-n-propylpyrazolo[1,5a]pyrimidine (30)

This compound was prepared from 1.75 g (0.01 mole) of the 5,7-dialkyl compound (mixed isomers), which was purified by chromatography on basic alumina with chloroform. A colorless oil was obtained and this soon solidified to white crystals, which upon recrystallization from benzene-petroleum ether (1:25) gave white needles, m.p. 88—89°C, 1.20 g (48%).

Anal. calcd for $C_{10}H_{12}N_3Br$ (MW 254): C, 47.24; H, 4.72; N, 16.53.
Found: C, 47.30; H, 4.81; N, 16.60.

NMR ($CDCl_3$) t, 1.05δ (propyl); m, 1.8δ (propyl); s, 2.64δ (C_5—CH_3); t, 3.10δ (propyl); s, 6.59δ (C_6—H); s, 8.05δ (C_2—H).

EXAMPLE XXIII.

7-Ethyl-5-methyl-3-nitropyrazolo[1,5a]pyrimidine (31)

Concentrated sulfuric acid (10 ml, sp. gr. 1.94) was cooled via ice bath and 3.2 g (0.02 mole) of the isomeric 7-(5)-ethyl-5(7)-methyl compound was cautiously added, with stirring. When the temperature remained at +15°C, concentrated nitric acid (7 ml, sp. gr. 1.35) was added dropwise, maintaining the temperature at +15°C throughout the addition. Then the solution was allowed to warm to room temperature and stirring was continued for 15—20 hours (overnight). The yellow solution was then cautiously poured over 200 g of ice, with stirring and the product precipitated. Filtration was difficult, so the product was extracted from the aqueous phase with methylene chloride (100 ml) and the organic layer was washed with water (100 ml) and dried (Na_2SO_4). Evaporation of the solvent yielded a dark semi-solid, fractionally recrystallized several times from methanol water to give 1.30 g of the pure 7-ethyl-5-methyl-3-nitro isomer, yellow needles, m.p. 127—128°C.

Anal. calcd for $C_9H_{10}N_4O_2$ (MW 206): C, 52.42; H, 4.85; N, 27.18.
Found: C, 52.45; H, 5.11; N, 27.11.

NMR (DMSO-d_6) t, 1.40δ ($C_{7'}$-ethyl); s, 2.70δ (C_5-methyl); q, 3.28δ ($C_{7'}$-ethyl); s, 7.35δ (C_7—H); s, 8.98δ (C_2—H).

EXAMPLE XXIV.

3-Carboethoxy-7-ethyl-5-methylpyrazolo[1,5a]pyrimidine (32)

This compound was prepared by refluxing 3.15 g (0.02 mole) of 3-amino-4-carbethoxypyrazole [C. C. Cheng, *J. Het. Chem.*, *5*, (1968) and J. Druey, P. Schmidt, *Chem. Abst.*, 53 10262e] and 2.3 g (0.02 mole) of hexane-2, 4-dione in ethanol (20 ml) with a catalytic amount of piperidine (2 drops) for 15—20 hours. The solvent was removed by distillation at reduced pressure (water aspirator) and the colorless oil remaining was triturated with ether-pentane, the solvent decanted, and the insoluble oil taken up in chloroform and chromatographed on basic alumina with chloroform. A colorless oil was obtained on evaporation of the solvent, and upon trituration with petroleum ether (30—60°) and ice bath cooling, white crystals, m.p. 33—38°C were obtained. The nmr spectrum ($CDCl_3$) indicated that both isomers were present, as suspected from the low, broad range of the melting point. Recrystallization several times from benzene gave 1.3 gm of the 7-ethyl-5-methyl isomer, free of the 7-methyl-5-ethyl isomer, m.p. 67—68°C.

Anal. calcd for $C_{12}H_{15}N_3O_2$ (MW 233): C, 61.78; H, 6.48; N, 18.02.
Found: C, 61.95; H, 6.60; N, 18.23.

NMR ($CDCl_3$) t, 1.43 (both terminal CH_3 of ethyl group and ethyl ester superimposed); s, 2.78 (C_5—CH_3); q, 4.45 (ethyl ester); s, 6.75 (C_6—H); s, 8.50 (C_2—H)

EXAMPLE XXV.

7-Methyl-5-phenylpyrazolo[1,5a]pyrimidine (33)

This compound was prepared from 1-phenylbutane-1,3-dione (8.1 g, 0.05 mol) in the usual manner, to give a crude product which was chromatographed on basic alumina with ether-chloroform (9:2) yielding white plates, 1.3 g (12.7%), m.p. 70—71° after recrystallization from petroleum ether. This product was demonstrated to be the pure 7-methyl-5-phenyl isomer by nmr.

Anal. calcd for $C_{13}H_{11}N_3$ (MW 209.3): C, 74.62; 5.30; N, 20.08.
Found: C, 74.77; H, 5.20; N, 20.21.

NMR ($CDCl_3$): s, 2.82 (C_7—CH_3); coupled s, 6.71 (C_6—H); s, 7.10 (C_6—H) m, 7.80 and 8.15 (C_7-phenyl ABX pattern) and coupled s, 8.03 (C_2—H). $J_{2,3}$=2.1 cps.

EXAMPLE XXVI.

5-Methyl-7-hydroxypyrazolo[1,5a]pyrimidine (34)

This compound was prepared from 3-aminopyrazole (1) and ethylacetoacetate, refluxing in ethanol with a catalytic amount of piperidine, in the same method as described by Y. Makisumi [*Chem. and Pharm. Bull. Japan*, *10*, 612 (1962)]. Yield: 80%, white powder, m.p. 297—298°C (lit. 298°C).

EXAMPLE XXVII.

3-Ethyl-7-hydroxy-5-methylpyrazolo[1,5a]pyrimidine (35)

A solution of ethyl acetoacetate [14.6 g (0.112 moles)] and 3-amino-4-ethylpyrazole (compound 5) [12.0g; 0.108 moles] was stirred at room temperature for 10 minutes and then diluted by adding 100 ml of glacial acetic acid. The resulting mixture was stirred and heated at reflux for 3 hours and then allowed to cool to room temperature. The mixture was added to 200 ml of ethyl acetate and the products separated by filtration. The solid products were separated by filtration and purified by recrystallization from aqueous ethanol to afford 14.7 g (77%), the analytically pure product that had a melting point of 290—2°.

Anal. Corresponds to that calc'd for ($C_9H_{11}N_3O_2$) C, H, N.

EXAMPLE XXVIII.

5-Methyl-7-chloropyrazolo[1,5a]pyrimidine (36)

This compound was prepared from the corresponding 7-hydroxy derivative in refluxing phosphorus oxychloride, in the prescribed manner of Y. Makisumi (ibid.) The product was purified by sublimation and recrystallization from petroleum ether. Yield: 20% on a large scale (0.5 mole) chlorination, colorless needles with a musty odor, m.p. 39—40°C. (lit. 40°C).

EXAMPLE XXIX.

7-Chloro-3-ethyl-5-methylpyrazolo[1,5a]pyrimidine (36a)

A suspension of 3-ethyl-7-hydroxy-5-methyl-pyrazolo[1,5a]pyrimidine (35)

[8.85 g (50 mmoles)] and 10 ml of N,N-dimethylaniline in 100 ml of phosphorous oxychloride was stirred and heated at reflux for 1 hour. At the end of this time, the excess phosphorous oxychloride was removed *in vacuo*, utilizing the steam bath as the source of heat. The residual syrup was added slowly with good stirring to 200g of crushed ice. The resulting solution was extracted with absolute ether 3(150 ml), and the combined etheral extracts were washed with sodium bicarbonate solution 3(100 ml) and then with water (100 ml). The etheral extract was dried over anhydrous sodium sulfate and then evaporated to dryness. The resulting crude chloro derivative were purified by recrystallization from *n*-heptane and then by vacuum sublimation at 120—140° (0.1mm) to afford 8.6 g (90%) of analytically pure product that had a melting point of 61—2°.

Anal. Corresponds to that calc'd ($C_9H_{10}N_3Cl$) N.

EXAMPLE XXX.

7-Diethylamino-5-methylpyrazolo[1,5a]pyrimidine (37)

This compound was prepared from 840 mg (0.005 mole) of the 7-chloro compound (36) and 730 mg (0.010 mole) of diethylamine. The product was isolated in the usual manner to yield 700 mg (69%) yellowish plates, m.p. 75—77°C from methanol-water.

Anal. Calcd for $C_{11}H_{16}N_4$ (MW 204.27) C, 64.67; H, 7.90; N, 27.43.
Found: C, 64.31; H, 8.05; N, 27.22.

EXAMPLE XXXI.

5-Methyl-7-piperidinopyrazolo[1,5a]pyrimidine (38)

This compound was prepared from 840 mg (0.005 mole) of the 7-chloro precursor (36) and 840 mg (0.010 mole) piperidine to yield 840 mg (78% yield) ivory colored platelets, m.p. 78—79°C from ethanol-water.

Anal. Calcd for $C_{12}H_{16}N_4$ (MW 216.28) C, 66.64; H, 7.46; N, 25.91.
Found: C, 66.93; H, 7.52; N, 26.14.

Mass Spectrum M^+=216 UV (MeOH) λ max (log εmax) at 225 (4.50), 2.80* (3.64), 290* (3.73), 320 (3.94) mμ.

EXAMPLE XXXII.

5-Methyl-7-n-Octylaminopyrazolo[1,5a]pyrimidine (39)

This compound was prepared from 840 mg (0.005 mole) of the analogous 7-chloro-5-methyl compound (36) and 1.30 g (0.010 mole) of n-octylamine to yield 255 mg (38%) white platelets, m.p. 48—50°C.

Anal. Calcd for $C_{15}H_{24}N_4$ (MW 260.37) C, 69.19; H, 9.29; N, 21.52.
Found: C, 69.28; H, 9.31; N, 21.71.

EXAMPLE XXXIII.

7-Hydrazino-5-methylpyrazolo[1,5a]pyrimidine (40)

This compound was prepared from 1.0 g of the 7-chloro derivative (36), which was refluxed in 30 ml ethanol containing 6 ml of 85% hydrazine hydrate. After 2 hours of reflux, the solution was concentrated to 10 ml (rotovap) whereupon the product separated as crystals. The material was washed with 5 ml cold ethanol to yield 420 mg of white plates, m.p. 228—230° dec. An analyticalproduct was recrystallized from ethanol.

Anal. Calcd for $C_7H_9N_5$ (MW 163.16) C, 51.50; H, 5.57; N, 42.92.
Found: C, 51.55; H, 5.61; N, 43.20.

NMR (d_6-DMSO) s, 2.44δ (CH_5—CH_3); s, 4.72δ (hydrazino NH); 2, 6.26δ coupled (C_3—H) to s, 8.03δ (C_2—H); s, 6.33δ (C_6—H); broad s, 8.82δ (hydrazino NH). Coupling constant $J_{2,3}$=2.5 cps.

EXAMPLE XXXIV.

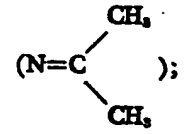
7-(2-N,N'-Isopropylidenehydrazino-5-methylpyrazolo[1,5a]pyrimidine (41)

A mixture of 1.1 g of the corresponding 7-hydrazino compound (40), 100 ml reagent grade acetone, and 20 ml of ethanolic hydrogen chloride was refluxed for 4 hours. Upon cooling, the insoluble material was filtered off and recrystallized from ethanol, m.p. 257—258°C (yield 20%).

Anal. Calcd for $C_{20}H_{27}N_{10}Cl$ (MW 442.5) hemihydrochloride C, 54.23; H, 6.10; N, 31.63; Cl, 8.02.
Found: C, 54.01; H, 6.32; N, 31.44; Cl, 7.86.

NMR (trifluoroacetic acid): s, 2.58δ (C_5—H); s, 2.88δ

* shoulder



s, 7.68 (C_3—H) coupled to s, 8.68 (C_2—H); s, 7.28 (C_6—H). $J_{2,5}$=2.5 cps.

EXAMPLE XXXV.

7-B-Hydroxyethylamino-5-methylpyrazolo[1,5a]pyrimidine (42)

This compound was prepared from 3000 mg of the corresponding 7-chloro compound (36), refluxed for 3 hours in 10 ml ethanol containing 100 mg of 2-aminoethanol (monoethanolamine). Evaporation of the solution (rotovap) and recrystallization of the solid residue from methanolether afforder 175 mg of yellow-white cubes, m.p. 162—163°C. The compound was found to be quite hygroscopic.

Anal. Calcd for $C_9H_{12}N_4O$ (MW 164.20) C, 65.83; H, 7.37; N, 17.06. Found: C, 65.37; H, 7.42; N, 17.23

NMR (d_6-DMSO) s, 2.40δ (C_5—CH_3); m, 3.4δ to 3.75δ (—CH_2—CH_2— of amine function); broad s, 5.0δ (OH); s, 6.12δ (C_6—H); s, 6.31δ (C_3—H) coupled to s, 8.05δ (C_2—H); broad s, 7.55δ (NH).

EXAMPLE XXXVI.

N-[5-methylpyrazolo[1,5a]pyrimidine-7-yl] glycine (43)

300 mg of the 7-chloro precursor (36) was dissolved in 10 ml of ethanol and mixed with 130 mg of glycine (18 mmol) dissolved in an aqueous solution of 200 mg sodium carbonate (19 mmol) in 20 ml water. The mixture was refluxed for 3 hours, then chilled to produce 200 mg of white platelets. Recrystallization from dimethylformamide-methanol gave crystals with mop. 305—305.5° dec.

Anal. Calcd for $C_9H_{10}N_4O_2$ (MW 206.20) C, 52.42; H, 4.89; N, 27.17. Found: C, 52.30; H, 4.98; N, 26.92.

EXAMPLE XXXVII.

3-Ethyl-5-methyl-7-n-propylaminopyrazolo[1,5a]pyrimidine (45)

A solution of 7-chloro-3-ethyl-5-methyl-pyrazolo[1,5a]pyrimidine (37) [0.585 g, (3 mmoles)] and *n*-propylamine [0.35 g; 6 mmoles] in 20 ml of absolute ethanol was stirred at room temperature for 2 hours. At the end of this time, the solution was evaporated to dryness and the residue titrated with 30 ml of water. Recrystallization of the residue from aqueous ethanol afforded 0.425 g (64%) the analytically pure product that had a melting point of 46—8°.

Anal. Corresponds to that calcd for ($C_{12}H_{18}N_4$) C, H, N.

EXAMPLE XXXVIII.

3-Ethyl-5-methyl-7-*n*-propoxypyrazolo[1,5a]pyrimidine (46)

A solution of sodium *n*-propoxide was prepared by dissolving sodium metal [0.165 g; 0.0072 formula weights] in 40 ml of *n*-propanol. This solution was stirred at room temperature and the 7-chloro-3-ethyl-5-methylpyrazolo[1,5a]pyrimidine (37) [1.29 g, (6.6 mmoles)] was added. The resultant solution was stirred at room temperature for 1 hour and then evaporated to dryness *in vacuo* at room temperature. The residue was extracted with boiling 60—90° petroleum ether 3(15 ml), and the combined extracts were evaporated to dryness to yield crude 3-ethyl-7-(*n*-propoxy)-5-methylpyrazolo[1,5a]pyrimidine (46). The produce was purified by column chromatography on silica gel (100g), utilizing a solvent system of 60—90° petroleum ether: ethyl acetate (8:2) to afford 1.11 g (77%) the analytically pure product that had a melting point of 92—4°.

Anal. Corresponds to that calcd for ($C_{12}H_{17}N_3O$) C, H, N.

EXAMPLE XXXIX.

3-Ethyl-7-ethylthio-5-methylpyrazolo 1,5a pyrimidines (47)

Ethanethiol [0.5g; 8.06 mmoles] was added to a solution of sodium metal [0.165g; 0.0072 formula weights] in 15 ml of anhydrous methanol. The resulting solution was stirred at room temperature for 20 minutes, and then the 7-chloro-3-ethyl-5-methylpyrazolo[1,5a]pyrimidine (37) [1.29 g (6.6 mmoles)] was added. The resulting solution was stirred at room temperature and then evaporated to dryness *in vacuo* at 25°C. The residue was extracted with boiling 60—90° petroleum ether

3(10 ml), and the combined extracts were evaporated to yield crude 3-ethyl-7-ethylthio-5-methylpyrazolo[1,5a]pyrimidine (47). The produce was purified by column chromatography on silica gel (100g), utilizing a solvent system of 60—90° petroleum ether:ethyl acetate (9:1) to yield the analytically pure product that was isolated as an oil.

Anal. Corresponds to that calcd for ($C_{11}H_{15}N_3S$) C, H, N.

EXAMPLE XL.

3-Bromo-7-n-butylamino-5-methylpyrazolo[1,5a]pyrimidine (48)

The 7 - n - butylamino - 5 - methylpyrazolo[1,5a]pyrimidine was prepared from 1.68 g (0.01 mole) of the corresponding 7-chloro-5-methyl compound and 1.46 g (0.02 mole) n-butylamine, and the oil obtained on work-up was utilized for bromination without further identification (other than spectra). The bromination procedure was the same as that employed for the 5,7-dialkylpyrazolo [1,5a] pyrimidines and upon work-up in the usual manner, with recrystallization from ether-petroleum ether, the 3-bromo compound was obtained as white platelets, m.p. 99—100°C, 1.41 g (50%).

Anal. Calcd for $C_{11}H_{15}N_4O_2Br$ (MW 315.21) C, 41.90; H, 4.76; N, 17.77; Br, 25.39.

Found: C, 42.16; H, 4.85; N, 17.92; Br, 25.11.

NMR ($CDCl_3$) exhibits peaks at s, 2.58δ (C_6—CH_3); s, 5.87δ (C_6—H); s, 7.92δ (C_2—H).

EXAMPLE XLI.

3-Bromo-7-(2,2'-dimethoxyethylamino)-5-methylpyrazolo[1,5a]pyrimidine (49)

This compound was prepared in a manner similar to that of the preceding compound, by reacting the 7-chloro-5-methyl derivative (1.68 g, 0.01 mole) with aminoacetaldehyde dimethylacetal (2.3 g, 0.021 mole) in ethanol, isolating the liquid 7-(2,2'-dimethoxyethylamino) derivative and brominating the oil with N-bromosuccinimide (1.78 g, 0.01 mole) in 50 ml chloroform and isolating the product as in the preceding example. Recrystallization of the chromatographed solid (chloroform on Merck basic alumina) gave pale ivory colored cubettes, 2.5 g, (79%), m.p. 134—135°C from petroleum ether (MERCK is a Registered Trade Mark).

Anal. Calcd for $C_{11}H_{15}N_4O_2Br$ (MW 315.21) C, 41.90; H, 4.76; N, 17.77; Br, 2539.

Found: C, 42.16; H, 4.85; N, 17.92; Br, 25.11.

NMR ($CDCl_3$) exhibits peaks at s, 2.58δ (C_6—CH_3); s, 5.87δ (C_6—H); s, 7.92δ (C_2—H).

EXAMPLE XLII.

The compounds of the invention were tested for inhibition of phosphodiesterase by the following procedure.

3',5'-Cyclic-AMP phosphodiesterase (PDE) was isolated and purified from three different tissues in the following manner. Homogenates of rabbit kidney, rabbit lung and beef heart are made in sucrose-Tris-magnesium buffer and are subjected to centrifugation at low speed to remove nuclei and cell debris. The supernatants are then centrifuged at 105,000 x g for 30 minutes, and the 105,000 x g supernatants are then fractionated using $(NH_4)_2SO_4$. The precipitation which forms at 0—30% saturation is collected by centrifugation at 20,000 x g, dissolved in Tris-magnesium buffer, and dialyzed overnight against the same buffer. A second $(NH_4)_2SO_4$ fraction is obtained by raising the concentration of the first supernatant to 50%. These two $(NH_4)_2SO_4$ fractions as well as the supernatant from the 30—50% cut were then assayed for PDE activity using the method of Appleman, *Biochem. 10,* 311 (1971). The first fraction obtained from both kidney and lung tissue contains a PDE with low affinity for 3',5'-c-AMP (high Km). The second fraction exhibits a bisphasic curve when the Lineweaver-Burk method of analysis is used. This indicates either the presence of two separate enzymes, one having a high and the other a low affinity for C—AMP, or one protein with two separate sites. Appleman, *supra,* indicates that extracts of brain yield two separate enzymes (a high Km and a low Km) which can be separated by sepharose gel chromatography.

The inhibitory studies reported in Tables I and II were performed with the low affinity (Fraction I, high Km) enzyme obtained from rabbit kidney or rabbit lung. The studies reported in Tables III—VI were performed with the high affinity (Fraction II, low Km) enzyme obtained from rabbit lung or kidney and beef heart. I_{50} values

were calculated in some instances from a plot of long I *vs.* percent I in experiments in which inhibitor concentration is varied over a wide range, at a constant 3',5'-cyclic AMP concentration of approximately $5 \times 10^{-4}M$ (Tables I and II) or $1.6 \times 10^{-7}M$ (Tables III and IV). The relative inhibitory activity of each compound as compared with theophylline is expressed as an α value. This value is obtained by dividing the I_{50} value obtained for the particular compound being evaluated.

In most instances, α values were calculated from an inhibition study performed with a single concentration of test compound as long as the inhibition produced by that concentration was from 20—80%. In this instance an α value was calculated as

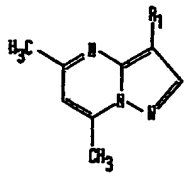
$$\frac{\text{concentration of theophylline giving (X\%) inhibition}}{\text{concentration of text substance giving the same (X\%) inhibition}}$$

The validity of this method has been checked by comparing α values obtained by (1) measurements at a single concentration of inhibitor and (2) measurements at four concentrations of inhibitor (I_{50} determinations). α values compared in this way have been found to agree to within 10% of each other.

The basic incubation mixture contained the following substances (amounts in μmoles): ^{3}H-cAMP (specific activity ~2,180 cmp/pmole), .00016; Tris pH 7.5, 40; $MgCl_2$, 0.5; Enzyme (cAMPphosphodiesterase), 5—50 μg protein; and 10^{-4} to 10^{-5} molar concentration of the inhibitor; incubation time 10 minutes at 30°C. At the end of incubation, the mixtures are heated to 90°C for 2 minutes and 100 μg of snake venom phosphodiesterase from Crotalus atrox was added and the tubes incubated for 10 minutes at 30°C. The mixture was then cooled and 1 ml of Dowex 1—2X, 200—400 mesh suspension, prepared by mixing 100 g of the resin in 200 G H_2O, was added and the mixture centrifuged. (DOWEX is a Registered Trade Mark.) An aliquot of the supernatant was used to determine counts per minute using a liquid scintillation spectrometer. Zero time values were obtained using incubations in which the cAMP phosphodiesterase was omitted from the first incubation.

TABLE I

Inhibition of 3′, 5′-Cyclic AMP Phosphodiesterase (PDE) Isolated from Rabbit Kidney

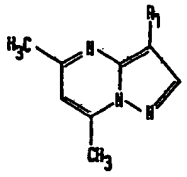


R_1	I_{50} [M]	I_{50} (theophylline) [M]	$\alpha = \frac{I_{50}\text{ (theophylline) [M]}}{I_{50}\text{ (compound) [M]}}$
H*	8×10^{-4}	1.6×10^{-4}	0.20
$COOC_2H_5$*	1×10^{-3}	2.2×10^{-4}	0.22
COMPOUND *1**	1.6×10^{-3}	2.2×10^{-4}	0.14
CN	2.5×10^{-4}	2.2×10^{-4}	0.88
$CONH_2$	3.4×10^{-4}	2.2×10^{-4}	0.65
CH_2NH_2	6×10^{-3}	2.2×10^{-4}	0.04
Br	1.0×10^{-4}	2.2×10^{-4}	2.20
Cl	2.4×10^{-4}	3.2×10^{-4}	1.33
I	1.3×10^{-4}	1.6×10^{-4}	1.23
$COCH_3$	2.8×10^{-4}	1.6×10^{-4}	0.57
$CH_2N(CH_3)_2$	4.3×10^{-4}	2.6×10^{-4}	0.61
NO_2	1.3×10^{-4}	2.2×10^{-4}	0.17
NH_2	2.5×10^{-3}	2.2×10^{-4}	0.09
$NHCOCH_3$	6×10^{-3}	2.2×10^{-4}	0.04

*For comparison only.

TABLE II

Inhibition of 3′, 5′-Cyclic AMP Phosphodiesterase (PDE) Isolated from Rabbit Lung

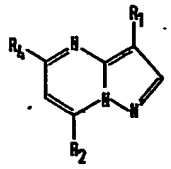


R_1	I_{50} [M]	I_{50} (Theophylline) [M]	$\frac{I_{50}\text{ (Theophylline) [M]}}{I_{50}\text{(Compound) [M]}}$ =
H*	2.0×10^{-3}	6.4×10^{-4}	0.32
CN	9.5×10^{-4}	6.5×10^{-4}	0.68
$CONH_2$	2.0×10^{-3}	6.5×10^{-4}	0.32
Br	2.7×10^{-4}	6.4×10^{-4}	2.4
Cl	2.1×10^{-4}	6.5×10^{-4}	3.1
I	2.1×10^{-4}	7.4×10^{-4}	3.5
$COCH_3$	5.0×10^{-4}	7.4×10^{-4}	1.5
$CH_2N(CH_3)_2$	1.3×10^{-3}	7.4×10^{-4}	0.57

*For comparison only.

TABLE III

5,7-dialkyl-3-substituted pyrazolo[1,5a]pyrimidines

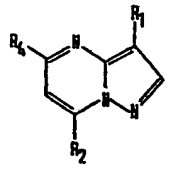


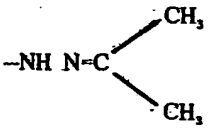
R_4	R_2	R_1	α Lung	α Heart
CH_3	CH_3	H*	0.3	0.2
CH_3	CH_3	COOEt*	0.6	0.4
CH_3	CH_3	$CONH_2$	0.5	0.4
CH_3	CH_3	CH_2NH_2		
CH_3	CH_3	Br	0.7	1.7
CH_3	CH_3	Cl	2.2	1.7
CH_3	CH_3	I	3.5	1.5
CH_3	CH_3	$COOCH_3$	1.0	0.4
CH_3	CH_3	$CH_2N(CH_3)_2$	0.3	0.3
CH_3	CH_3	NO_2	0.4	0.2
CH_3	CH_3	NH_2		
CH_3	CH_3	$NHCOCH_3$	0.1	0.1
CH_3	CH_3	C_2H_5	2.2	
CH_3	CH_2–CH_2–CH_3	H	2.1	1.1
CH_3	–CH_2–CH_2–CH_3	Br	7.5	6.5
CH_2–CH_3	–CH_2–CH_3	H	3.0	1.1
CH_3	–CH_2–CH_3	$COOC_2H_5$	1.5	0.5
CH_2–CH_3	CH_2–CH_3	Br	7.4	6.0
CH_2–CH_2–CH_3	–CH_2–CH_2–CH_3	Br	5.5	3.0
CH_3	CH_2–CH_3	Br	7.5	4.0
CH_3	CH_2–CH_3	NO_2	2.5	0.5
C_6H_5	CH_3	H	3.4	2.4
CH_2–CH_2–CH_3	CH_2–CH_2–CH_3	H		

* For comparison only.

TABLE IV

5-Alkyl-3,7-disubstituted pyrazolo[1,5a] pyrimidines



R_4	R_2	R_1	PDE aLung	PDE aHeart
CH_3	$NH-CH_2-CH_2-CH_3$	C_2H_5	9.4	–
CH_3	$O-CH_2-CH_2-CH_3$	C_2H_5	5.4	–
CH_3	$S-CH_2-CH_3$	C_2H_5	8.9	–
CH_3	$NH-CH_2-CH_2-CH_2-CH_3$	Br	1.5	6.0
CH_3	$NH-CH_2-CH_2(OCH_3)_2$	Br	6.8	4.5
CH_3	$N(C_2H_5)2$	H	3.2	1.7
CH_3		H	2.4	1.5
CH_3	$NH(CH)_7-CH_3$	H	9.0	3.0
CH_3	$NH-NH_2$	H	1.5	0.5
CH_3		H	–	–
CH_3	$NH-CH_2-CH_2OH$	H	0.5	3.7
CH_3	$NH-CH_2-COOH$	H	0.2	2.1
CH_3	$-O-CH_2-CH_3$ *	H	1.4	1.0

* For comparison only.

The results shown in the foregoing Tables indicate that several of the compounds of this invention are several times more effective as inhibitors of phosphodiesterase enzyme than theophylline. By the same token, the results indicate that these compounds are capable of selective inhibition. It should also be noted that other examples could be given of compounds within the scope of the present invention, as for example, compounds where R_1 is an alkyl other than ethyl (in which case, the compounds would be prepared by the procedure of the foregoing corresponding Examples, using another alkyl nitrile as a starting material in place of *n*-butyronitrile or ethyl benzoylacetate in place of ethyl acetoacetate) with similar satisfactory results to be obtained. For the sake of brevity of disclosure, however, additional example will not be provided herein.

In general, the phosphodiesterase inhibitors of the invention may find employment in the treatment of disorders responsive to the administration of epinephrine or norepinephrine, since in either case the result is maintenance of greater levels of C—AMP — in the first instance by retarding C—AMP degradation and in the second by stimulating its production.

Several compounds of the invention have been tested *in vivo* and reveal a variety of activities indicative of selective transport to specific tissues. Thus 3-cyano-5,7-dimethyl pyrazolo[1,5a]pyrimidine has been shown to significantly inhibit ADP-induced platelet aggregation. The corresponding 3-nitro analog exhibits anti-pregnancy effect at 25 and 12.5 mg/kg orally, appreciable anti-edema activity, and some inhibition of ADP-induced platelet aggregation. The 3-carboxamido analog of these compounds similarly demonstrated an anti-edema effect and was very active against ADP-induced platelet aggregation. 5,7-Dimethyl-3-bromo pyrazolo[1,5a]pyrimidine exhibited anti-edema and ADP-induced platelet aggregation inhibitory effects, and additionally had muscle relaxant properties at 300 mg/kg 3 hours after administration. This compound also exhibits a positive inotropic effect on the heart. It is interesting to note that the known compound 5,7 - dimethyl - 3 - carbethoxy pyrazole [1,5a]pyrimidine was an anticonvulsant at 100 mg/kg, as well as an inhibitor of ADP-induced platelet aggregation.

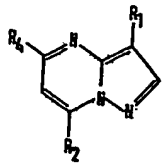
Preliminary pharmacological evaluation has revealed that 5,7-dimethylpyrazolo-[1,5a]pyrimidine - 3 - carboxamide, 5,7 - dimethyl - 3 - iodopyrazolo[1,5a]pyrimidine, 3 - bromo - 5,7 - dimethylpyrazolo[1,5a]pyrimidine, and 5 - isopropylpyrazolo[1,5a]pyrimidin - 7 - ol possess significant cardiovascular properties. In the isolated Langendorf heart preparation, these compounds bring about coronary dilation and/or produce a positive inotropic effect at concentrations of 2.5 mg/ml.

When administered orally to rats at a dose of 50 mg/kg of body weight, 5,7-dimethylpyrazolo[1,5a]pyrimidine - 3 - carboxamide, 3 - bromo - 5,7 - dimethylpyrazolo[1,5a]pyrimidine, 5,7 - dimethyl - 3 - iodopyrazolo[1,5a]pyrimidine, and 5 - isopropylpyrazolo[1,5a]pyrimidin - 7 - ol significantly lowered blood pressure (10% or more). At an oral dose of 25 mg/kg, 5,7 - dimethyl - 3 - iodopyrazolo[1,5a] pyrimidine lowered blood pressure by 10% for periods of up to six hours.

In anesthesized dogs, 3 - bromo - 5,7 - dimethylpyrazolo[1,5a] pyrimidine [5 mg/kg; i.v. infusion] caused a significant increase in the cardiac output at both 30 and 60 minutes following the start of infusion (p 0.05). The increased output was 21% and 20% respectively. The cardiac output was maintained above baseline values for two hours after the infusion was stopped. A similar increase ($p=0.005$) was observed in stroke volume during the same time. No significant changes were noted in the arterial pressure, central venous pressure, or heart rate.

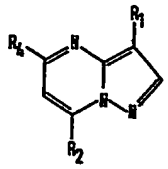
Additional pharmacological evaluation has revealed that 5,7 - dimethyl - 3 - nitropyrazolo[1,5a] pyrimidine and 7 - hydrazino - 5 - methylpyrazolo[1,5a] pyrimidine possess anti-pregnancy activity in mice at an oral dose of 12.5 mg/kg of body weight.

Numerous of the 3,5,7-trisubstitutedpyrazolo[1,5a] pyrimidines have shown anti-inflammatory (anti-edema) activity when evaluated by the methods described by C. A. Winter, et al, in *Proc. Exper. Biol. Med., 111,* 544 (1962). In this test procedure significance is associated with compounds that bring about at least a 30% reduction in foot volume when administered orally to rats at an oral dose of 100 mg/kg of body weight. The following table illustrated the activity possessed by various compounds of the present invention.



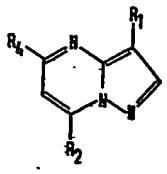
R_4	R_2	R_1	Dose mg/kg	Inhibition of foot volume (%)
CH_3	CH_3	NO_2	100	30
CH_3	CH_3	$CONH_2$	100	38
,,	,,	,,	50	0
CH_3	CH_3	Br	100	38
,,	,,	,,	50	10
CH_3	CH_3	I	100	75
,,	,,	,,	50	54
,,	,,	,,	25	0
CH_3	$NH-C_4H_9(n)$	Br	100	50
,,	,,	,,	50	0

Numerous of these 3,5,7-trisubstitutedpyrazolo[1,5a]pyrimidines are classified as smooth muscle relaxants as evidenced by the fact that relaxation of isolated guinea pig uteri preparations is observed on administration of such a compound. The following table illustrates the activity that various compounds of the present invention possess (Significance is associated with a + response at concentrations of 10 mg/ml or less).



R_4	R_2	R_1	Conc. μg/ml	Response
CH_3	CH_3	I	10	+
,,	,,	,,	2	+
,,	,,	,,	0.4	−
$CH(CH_3)_2$	OH	H	10	+
,,	,,	,,	2	−
C_6H_5	CH_3	H	10	+
,,	,,	,,	2	+
,,	,,	,,	0.4	−
$C_3H_7(n)$	$C_3H_7(n)$	H	10	+
,,	,,	,,	2	+
,,	,,	,,	0.4	−
C_2H_5	C_2H_5	H	10	+
,,	,,	,,	2	−
CH_3	$C_3H_7(n)$	Br	10	+
,,	,,	,,	2	+
,,	,,	,,	0.4	−
$C_3H_7(n)$	$C_3H_7(n)$	Br	10	+
,,	,,	,,	2	−

Numerous of the 3,5,7-trisubstitutedpyrazolo[1,5a]pyrimidines have also been found to significanty inhibit ADP induced platelet aggregation as determined by the method of M. H. Pindell, et al, described in *Microvasc. Research, 1,* 374 (1969). Significance in this test system is associated with compounds that possess the ability to inhibit 50% or greater at a concentration of 100 mg/ml. The following table illustrates the activity that various compounds of the present invention possess.



R_4	R_2	R_1	Conc. μg/ml	(%) Inhibition
CH_3	CH_3	C≡N	100	79
,,	,,	,,	50	62
,,	,,	,,	25	31
CH_3	CH_3	NO_2	100	54
,,	,,	,,	50	41
CH_3	CH_3	$CONH_2$	100	100
,,	,,	,,	10	51
,,	,,	,,	5	41
CH_3	CH_3	COOEt*	100	59
,,	,,	,, *	50	21
CH_3	CH_3	Br	100	75
,,	,,	,,	50	50
CH_3	C_2H_5	NO_2	100	72
,,	,,	,,	50	16

* For comparison only.

When 3 - ethyl - 5 - methyl - 7 - *n* - propylaminopyrazolo[1,5a]pyrimidine was administered orally to rats at a dose of 100 mg/kg, it was observed that this compound possessed significant anti-inflammatory activity. Following the protocol of C. A. Winter, et al, described in *Proc. Exper. Biol. Med., 111,* 544—7 (1962), this compound brought about a 30—40% decrease in foot volume as adjudged 4 hours after dosing.

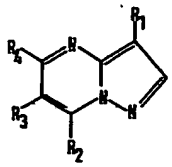
A. B. Richards, et al, described in *Curr. Ther. Res., 11,* 587—93 (1963) a method for evaluating compounds for their antinauseant activities. Following this protocol, it has been found that 5,7 - dimethyl - 3 - ethylpyrazolo[1,5a]pyrimidin-7 - yl) - N,N - dimethyl hydrazine possess significant antinauseant activity when administered by intraperitoneal injection to guinea pigs at a dose of 100 mg/kg of body weight.

When 5,7 - dimethyl - 3 - ethylpyrazolo[1,5a]pyrimidine was administered orally to rats at a dose of 25 mg/kg, it was observed that this compound possessed the ability to inhibit stress induced ulcer formation. Following the procedures described by D. A. Brodie, et al, in *Journal of Neuropsychiatry, 4,* 388—408 (1968), this compound inhibited stress induced ulcers by 60—70% six hours after dosing.

Preliminary pharmacological evaluation has revealed also that several 3-alkyl substituted compounds of the present invention possess the ability to bring about

smooth muscle relaxation. Following the protocol described by B. Levy and S. Tozzi in *Journal of Pharmacology and Experimental Therapeutics, 142,* 178—84 (1963), it has been found that several of the compounds bring about relaxation of isolated guinea pig uteri at low concentrations. The results of these studies are summarized in Table VIII.

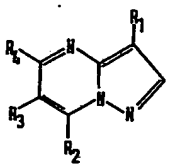
TABLE VIII



R_4	R_3	R_2	R_1	Minimum Effective Concentration (μg/ml)
CH_3	H	CH_3	C_2H_5	10
CH_3	H	$NH-CH_2-CH_2-CH_3$	C_2H_5	2
CH_3	H	$O-CH_2-CH_2-CH_3$	C_2H_5	10
CH_3	H	$S-CH_2-CH_3$	C_2H_5	10

WHAT WE CLAIM IS:—

1. A compound of the structure



wherein R_1 is H, alkoxycarbonyl, alkyl, carbonitrile, halogen, carbamoyl, acyl, aminomethyl, dialkylaminomethyl, nitro, amino, or acetamido; R_2 is alkyl, C_1 to C_8 linear or branched chain alkoxy, C_1 to C_6 alkylthio, SH, or alkyl or dialkylamino, cyclic amino or substituted amino; R_3 is H; and R_4 is H, alkyl, or phenyl; provided that when R_2 and R_4 are methyl, R_1 is not H or carbethoxy; when R_4 is CH_3 and R_2 is methoxy or ethoxy, R_1 is not H, when R_2 is CH_3, R_4 and R_1 are not both H; and when R_2 is hydrazine and R_4 is phenyl, R_1 is not H.

2. A compound as claimed in claim 1, wherein there is at least one alkyl substituent having from 1 to 8 carbon atoms.

3. A compound as claimed in claim 1 or claim 2, wherein there is at least one alkoxy substituent having from 1 to 4 carbon atoms.

4. A compound as claimed in any one of claims 1 to 3, wherein R_2 is an alkylthio group having from 1 to 3 carbon atoms.

5. A compound as claimed in any one of claims 1 to 3, wherein R_2 is dialkoxyalkylamino, carboxyalkylamino, hydroxyalkylamino, hydrazyl, alkylidenohydrazyl, morpholino or piperidino.

6. A compound as claimed in any one of claims 1 to 3, wherein R_2 and R_4 are alkyl and R_1 is halogen.

7. A compound as claimed in claim 6, wherein R_2 and R_4 are methyl and R_1 is bromine, chlorine or iodine.

8. A compound as claimed in claim 6, wherein R_4 is methyl, R_2 is propyl, and R_1 is halogen.

9. A compound as claimed in claim 8, wherein R_1 is bromine.

10. A compound as claimed in any one of claims 1 to 3, wherein R_2 and R_4 are alkyl and R_1 is H.

11. A compound as claimed in claim 10, wherein R_2 and R_4 are ethyl.

12. A compound as claimed in claim 6, wherein R_2 and R_4 are both ethyl or propyl and R_1 is bromine.

13. A compound as claimed in claim 6, wherein R_2 is ethyl, and R_1 is bromine.

14. A compound as claimed in any one of claims 1 to 3, wherein R_2 and R_4 are alkyl and R_1 is nitro.

15. A compound as claimed in claim 14, wherein R_4 is methyl and R_2 is ethyl.

16. A compound as claimed in any one of claims 1 to 3, wherein R_4 is phenyl, R_2 is alkyl and R_1 is H.

17. A compound as claimed in claim 16, wherein R_2 is methyl.

18. A compound as claimed in any one of claims 1 to 3, wherein R_4 is alkyl, R_2 is alkylamino and R_1 is halogen.

19. A compound as claimed in claim 18, wherein R_4 is methyl, R_2 is butylamino and R_1 is bromine.

20. A compound as claimed in any one of claims 1 to 3, wherein R_4 is alkyl, R_2 is alkylamino or dialkylamino, and R_1 is H.

21. A compound as claimed in claim 20, wherein R_4 is methyl and R_2 is diethylamino.

22. A compound as claimed in claim 21, wherein R_4 is methyl and R_2 is octylamino.

23. A compound as claimed in any one of claims 1 to 3 or 5, wherein R_4 is alkyl, R_2 is substituted amino and R_1 is halogen.

24. A compound as claimed in claim 23, wherein R_4 is methyl, R_2 is dialkoxyalkylamino, and R_1 is bromine.

25. A compound as claimed in claim 24, wherein R_2 is dimethoxyethylamino.

26. A compound as claimed in any one of claims 1 to 3 or 5, wherein R_4 is alkyl, R_2 is cyclic amino or substituted amino and R_1 is H.

27. A compound as claimed in claim 26, wherein R_4 is methyl and R_2 is piperidino or hydroxyalkylamino.

28. A compound as claimed in claim 27, wherein R_2 is hydroxyethylamino.

29. A compound as claimed in any one of claims 1 to 3, wherein R_1 is ethyl.

30. A compoud as claimed in claim 29, wherein R_2 and R_4 are methyl.

31. A compound as claimed in claim 29, wherein R_4 is methyl and R_2 is alkylamino.

32. A compound as claimed in claim 31, wherein R_2 is propylamino.

33. A compound as claimed in claim 29, wherein R_4 is methyl and R_2 is propoxy or ethylthio.

34. A process for preparing the 3,5,7 trisubstitutedpyrazolo[1,5a]pyrimidines defined in claim 1, which process comprises reacting a 3-aminopyrazole derivative with a symmetrical β-diketone or an unsymmetrical β-diketone.

35. A process as claimed in claim 34, wherein a 3-unsubstituted compound is obtained in the reaction involving a 3-amino-pyrazole derivative which 3-unsubstituted compound is subsequently reacted with an electrophilic reagent to obtain a 3,5,7-trisubstitutedpyrazolo [1,5a] pyrimidine.

36. A process as claimed in claim 35, wherein the electrophilic reagent is N-bromosuccinimide, N-chlorosuccinimide, iodine monochloride, trifluoroacetic acid and boron trifluoride etherate, a friedelcrafts acylation system, a nitrating reagent, or an aqueous solution of dimethylamine and formalin solution.

37. A process for preparing the 3,5,7-trisubstitutedpyrazolo[1,5-a]-pyrimidines defined in claim 1 which process comprises reacting a 3-aminopyrazole derivative with a β-keto ester, treating the resulting 7-hydroxy substituted compound with phosphorus oxychloride to obtain the 7-chloro-3,5-disubstituted pyrazolo [1,5-a] pyrimidine, which is then reacted with a nucleophilic reagent to provide the said 7-amino-, 7-alkoxy- or 7-alkylthio- derivatives.

38. A process as claimed in claim 37, wherein the nucleophilic reagent is an amine, a sodium alkoxide or a sodium alkylmercaptide.

39. A process as claimed in claim 34, substantially as hereinbefore described.

40. A process as claimed in claim 34, substantially as hereinbefore described in any one of the specific Examples.

41. A compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 34 to 40.

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34 Cursitor Street, London, EC4A 1PQ.
Chartered Patent Agents.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1975.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.